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ORIGINAL RESEARCH

Cardiology

Safety of prehospital intravenous bolus dose nitroglycerin in patients with acute pulmonary edema: A 4-year review

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Abstract

Background: Intravenous nitrates are a primary therapy for hypertensive congestive heart failure (CHF) with acute pulmonary edema (APE) in the hospital setting. Historically, sublingual nitrates are the mainstay of emergency medical services (EMS) pharmacologic therapy for these patients. We aimed to evaluate the safety of prehospital bolus dose intravenous nitroglycerin in patients with APE.

Methods: This is a retrospective evaluation of EMS data between March 15, 2018, and March 15, 2022, where CHF with APE was suspected and bolus-dose intravenous nitroglycerin was administered. Protocol inclusion criteria were hypertension (systolic blood pressure [SBP] >160 mmHg) and acute respiratory distress, with a presumption of decompensated CHF with APE. These patients received 1 mg intravenous nitroglycerin, with the option to repeat once for ongoing distress if the SBP remained >160 mmHg. The primary outcomes were adverse events, defined as hypotension (SBP <90 mmHg), syncope, vomiting, or dysrhythmia.

Results: The final analysis included 235 patients. In patients receiving intravenous bolus nitroglycerin, the median (interquartile range [IQR]) initial and final EMS SBP values decreased from 198 mmHg (180–218) to 168 (148–187), respectively. The median (IQR) pulse decreased from 108 (92–125) to 103 (86–119), and the median oxygen saturation increased from 89% (82–95) to 98% (96–99). Three episodes (1.3%) of asymptomatic hypotension occurred, and none required intervention.

Conclusion: This study supports a favorable safety profile for prehospital bolus-dose intravenous nitroglycerin for decompensated CHF with APE. Blood pressure, heart rate, and oxygen saturation improvements are also demonstrated. Further, prospective studies are needed to confirm these findings.

KEYWORDS
acute pulmonary edema, congestive heart failure, emergency medical services, nitroglycerin, prehospital

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1 | INTRODUCTION

1.1 | Background

The burden of congestive heart failure (CHF) has an enormous impact on approximately 6.6 million patients in the United States.[1] This number will likely increase as the population ages, further magnifying the reported CHF mortality rate of 25% within 6 months of hospital admission for an exacerbation.[2] The classification of various acute heart failure syndromes (AHFS) is heterogeneous, making clear definitions challenging.[3] However, the recognition of a specific class of AHFS with hypertension and acute pulmonary edema has been described with variable terminology, including sympathetic crashing acute pulmonary edema and hypertensive acute heart failure.[4,5] Although the incidence of acute pulmonary edema (APE) is difficult to measure, current estimates report that up to 16% of patients with AHFS have concurrent APE.[6]

1.2 | Importance

Promptly addressing preload and afterload in patients with decompensated hypertensive AHFS are the pillars of pharmacologic therapy.[7–9] Nitrate use during hospitalization for AHFS with APE improves mortality and morbidity,[10–14] and doses higher than sublingual doses typically administered (~0.8 mg) by emergency medical services (EMS) clinicians demonstrate increased efficacy in treating these critically ill patients.[15–17] However, studies have shown that prehospital sublingual nitroglycerin (NTG) therapy is still effective and safe.[17–18] Allowing paramedic use of intravenous NTG could offer advantages for EMS, as patients with APE who require non-invasive positive pressure ventilation (NIPPV) develop dry mucous membranes—making sublingual absorption difficult—and requires breaking of the mask's seal for each administered dose. We suspect improved patient outcomes could be obtained from EMS administration of intravenous NTG as it directly addresses both preload and afterload reduction, while allowing continuous NIPPV mask seal maintenance with concomitnant rapid medication delivery.[10,11,19,20]

1.3 | Goals of this study

In this study, we evaluated the safety profile of prehospital intravenous bolus NTG administration by paramedics for AHFS complicated by APE in a single high-volume, ground-based EMS agency.

2 | MATERIALS AND METHODS

2.1 | Study design and setting

We performed a retrospective evaluation of patient care reports between March 15, 2018, and March 15, 2022, from a suburban, county-based EMS service in Texas, in which AHFS with APE was suspected, and bolus-dose intravenous NTG was given. The data review was a quality improvement initiative on a previously implemented EMS protocol for treating decompensated AHFS with APE. The sponsoring EMS agency employs approximately 300 paramedics supported by 13 first responder organizations, which include over 1100 emergency medical technicians. The service area covers 1100 square miles and responds to more than 90,000 calls for service per year. The Baylor College of Medicine Institutional Review Board approved this study with a waiver of informed consent (H-43267).

The Bottom Line

The care of critical patients begins in the prehospital setting. Recent evidence demonstrated the safety and efficacy of high-dose nitroglycerin for hypertensive pulmonary edema patients in the emergency department. This retrospective evaluation of vital sign improvement following the treatment of hypertensive pulmonary edema with intravenous nitroglycerin shows a favorable safety profile for starting this care in the prehospital setting.

2.2 | Intervention

The protocol for decompensated AHFS complicated by APE used in this study is presented in Figure 1. Although classic CHF historical and physical exam findings were taught and included in the protocol, none of these was required beyond an overall clinical suspicion of APE due to AHFS. After identifying probable APE due to AHFS, paramedics slowly administered 1 mg of NTG intravenous or intraosseous. Additionally, they could administer sublingual NTG (0.4 mg) while intravenous/intraosseous access was in process, but intravenous treatment required a systolic blood pressure (SBP) >160 mmHg at the time of administration. A second 1 mg dose was allowed 5 min after the initial administration if the SBP remained >160 mmHg. The protocol permitted a maximal cumulative 2 mg dose. NIPPV was encouraged but not required. Similarly, advanced airway management was left to paramedic discretion.

All paramedic staff completed a mandatory 2-hour training session 1 month before protocol deployment, which coincided with the start of data collection. This session included an in-person lecture-style review of NTG pharmacology, instruction on the pathophysiology and clinical findings of decompensated AHFS with APE, and an introduction to the protocol specifics. Emphasis was placed on the role of bolus intravenous NTG in relation to the current treatment of AHFS with hypertensive APE and the differentiation of AHFS with APE from obstructive lung disease exacerbation. Historical, exam, and vital sign factors were targeted, including the acuity of onset, high-risk past medical history (hypertension, end-stage renal disease, and known CHF),

ACUTE CHF/ACUTE PULMONARY EDEMA TREATMENT PROTOCOL

Historical Findings	Physical Findings
▪ Prior history of CHF ▪ Orthopnea ▪ Paroxysmal nocturnal dyspnea ▪ Cocaine/Methamphetamine use	▪ Rales ▪ Pedal edema ▪ History of A-fib or A-fib on EKG

Assessment:

- Cardiac assessment
- DDX: Ischemia, HTN crisis, renal (fluid overload), non-cardiogenic (drowning, inhalational, drug-induced)

Clinical Management Options:

Interventions	Pharmacology
▪ Noninvasive ventilation ▪ 12-Lead ECG ▪ Vascular access ○ Consider IO on urgent/critical patient	▪ **NTG** 0.4 mg sublingual ○ If systolic >100mmHg ○ May repeat q 3-5 min x 3 prior to vascular access ○ May repeat q 3-5 min PRN following vascular access **AND IF MODERATE/SEVERE RESPIRATORY DISTRESS:** ▪ **NTG** 1mg slow IVP ○ Only if systolic >160 ○ May repeat x 1 q 5 minutes ○ Consider IV NTG in tandem with NIPPV

Consult:

- If DSI is needed

FIGURE 1 Acute CHF/acute pulmonary edema treatment protocol. Abbreviations: A-fib, atrial fibrillation; CHF, congestive heart failure; DSI, delayed sequence intubation; HTN, hypertension; IO, intraosseous; IVP, intravenous push; NIPPV, non-invasive positive pressure ventilation; NTG, nitroglycerin

presence of rales on auscultation, and waveform capnography use were all emphasized as considerations making AHFS with APE more likely in patients presenting with elevated blood pressure and moderate to severe respiratory distress. Paramedic demonstration of protocol understanding was verified via written and psychomotor testing after the initial mandatory education program. Lastly, the bolus intravenous NTG protocol was reinforced during the study period through multiple internally produced podcast episodes.

2.3 | Selection of participants

Patients who received intravenous bolus NTG during the study period were included in the data analysis. These patients were collected by querying the EMS electronic patient care record for all intravenous bolus NTG patients. Data sources were the prehospital electronic patient care record and EMS monitor data.

2.4 | Measures

Two expert paramedics abstracted data after a training session emphasizing the desired chart and narrative data needed. A standardized chart review form was used after a complete EMS chart review. Two emergency physicians adjudicated any variances. The primary outcomes were adverse events, defined as hypotension (SBP <90 mmHg), syncope, vomiting, or dysrhythmia. Hypotension and dysrhythmia were noted from the EMS vital signs, and syncope and vomiting were identified from the clinician narrative. Study variables recorded were demographic information, past medical history, and hemodynamic data throughout EMS transport. Specifically, the initial and final EMS blood pressures, heart rate, and oxygen saturation were collected and used for assessment. Additionally, data regarding NTG routes of administration, albuterol administration rates, 12-lead electrocardiogram assessment, on-scene and transport times, and NIPPV/intubation rates were collected. The timing of NIPPV and intubation relative to intravenous NTG administration was unavailable. Protocol violations were assessed for incorrect intravenous NTG dosing and administration outside of the defined SBP parameters.

2.5 | Data analysis

Microsoft Excel (Microsoft Corporation, Redmond, WA) and Stata IC Version 15.1 (StataCorp LLC, College Station, TX) were used to complete the analyses. Descriptive statistics were calculated, with median (interquartile range) presented for continuous variables and frequency (%) presented for categorical variables. Wilcoxon signed-rank tests

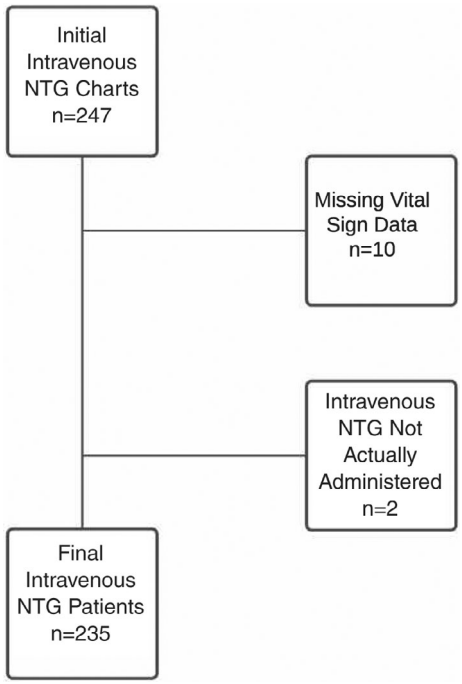

FIGURE 2 Bolus intravenous NTG chart inclusion/exclusion. Abbreviation: NTG, nitroglycerin.

were used to evaluate the median difference for paired data, and Wilcoxon rank-sum tests were used for unpaired data.

3 | RESULTS

Two hundred and forty-seven EMS patient charts satisfied the inclusion criteria and were reviewed. Twelve patients were removed from the analysis due to missing vital signs ($n = 10$) and inaccurate documentation of intravenous NTG administration ($n = 2$). As a result, the final study included 235 patients (Figure 2).

Study patients had a median age of 71 years old (62, 79), 58% were male, 81% white, and 58% and 69% had a past medical history of CHF and essential hypertension, respectively (Table 1). For these patients, EMS spent a median time on scene of 20 (15, 25) min, with a median transport time of 17 (12, 24) min. Albuterol was administered in 18% of cases (42/235), 69% (163/235) of patients were placed on NIPPV, and 8% (18/235) required intubation. Twenty-nine percent (67/235) of patients also received sublingual NTG before receiving intravenous NTG. Seventy-one percent (167/235) of patients received only 1 dose of parenteral NTG, whereas 26% (62/235) received a second parenteral dose (Table 2). Protocol non-compliance was noted in the remaining 3% (6/235) due to receiving a third parenteral dose (3 mg total). Another case reflected non-compliance with the protocol due to intravenous NTG having been given with a preadministration SBP of 159 mmHg—however, none of the protocol deviation cases developed hypotension.

Patients treated with intravenous bolus NTG had median initial and final EMS SBP values of 198 mmHg (180, 218) and 168 mmHg

TABLE 1 Demographic characteristics of patients treated ($n = 235$).

	Frequency (%)
Age, years	
Mean (SD)	70 (13)
Median (interquartile range)	71 (62–79)
Range	33–100
Sex	
Male	136 (58)
Female	99 (42)
Race or ethnicity	
White	190 (81)
Black	17 (7)
Hispanic	24 (10)
Asian	3 (1)
Other	2 (1)
Past medical history	
Congestive heart failure	137 (58)
Hypertension	161 (69)
Diabetes mellitus	85 (36)
End-stage renal disease	25 (11)

TABLE 2 Description of prehospital care provided ($n = 235$).

	Frequency (%)
Placed on NIPPV	163 (69)
Intubated by EMS	18 (8)
Received albuterol	42 (18)
Received prehospital 12-lead ECG	221 (94)
STEMI	2 (1)
Missing	14 (6)
Scene time, median (IQR)	20 min (15,25)
Transport time, median (IQR)	17 min (12,24)
Nitroglycerin dosage	
IV	235 (100)
1 mg	167 (71)
2 mg	62 (26)
3 mg	6 (3)
Sublingual (before IV)	67 (29)
0.4 mg	50 (21)
0.8 mg	16 (17)
1.2 mg	1 (1)

Abbreviations: EMS, emergency medical services; IQR, interquartile range; IV, intravenous; NIPPV, non-invasive positive pressure ventilation; STEMI, ST-elevation myocardial infarction.

TABLE 3 Vital signs before IV nitroglycerin administration and at presentation to the emergency department. Presented as median (IQR) ($p < 0.001$).

	Initial EMS	Final EMS	Median Change
Systolic blood pressure, mmHg	198 (180, 218)	168 (148, 187)	−28 (−51, −11)
Diastolic blood pressure, mmHg	106 (92, 125)	90 (79, 105)	−14 (−33, −1)
Heart rate, bpm	113 (96, 124)	103 (86, 118)	−5 (−12, 3)
Oxygen saturation, %	86 (74, 89)	98 (96, 99)	7 (1, 14)

Abbreviations: bpm, beats per minute; IV, intravenous.

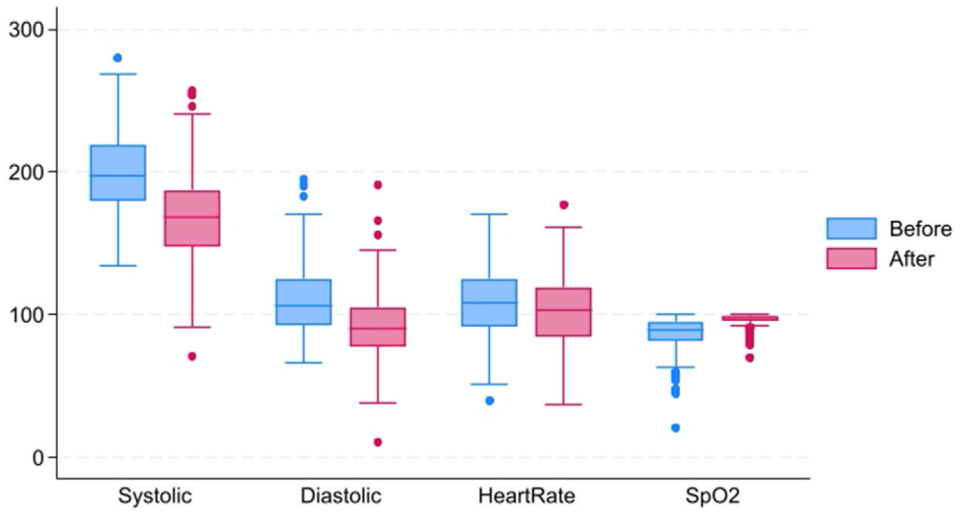

FIGURE 3 Vital signs before and after treatment.

(148, 187), respectively. After EMS administration of bolus intravenous NTG, the median pulse decreased from 113 (96, 124) to 103 (86, 18) beats per minute, and the median oxygen saturation increased from 86% (74–89) to 98% (96–99) (Table 3). An ECG was obtained in 94% (221/235) of patients, with ST-elevation myocardial infarction documented in 2 cases. Six percent (14/235) of cases had missing ECG data. The only adverse event reported after intravenous NTG administration was hypotension (<90 mmHg). The 3 hypotensive episodes were clinically asymptomatic based on narrative review. SBP, diastolic blood pressure, heart rate, and SpO_2 all differed significantly pre/post-treatment ($p < 0.001$). In the NIPPV and sublingual NTG subgroups, all vital signs were significantly different ($p < 0.001$) pre/post treatment except for heart rate in the group that received sublingual NTG but did not receive NIPPV ($n = 24$, $p = 0.49$) (Table 4).

4 | LIMITATIONS

This study used a single agency data source and a retrospective study design. Without a control group or exact timing, it was not possible to assess the impact of bolus intravenous NTG treatment on the use of NIPPV, prehospital intubation, or patient mortality. These are significant concerns, as hospital-based studies have shown that intravenous NTG decreases the need for intubation and mechanical ventilation.[6,10–13] Highlighting similar EMS findings would solidify the benefit of initiating this therapy in the prehospital setting. Lastly, this study occurred during the COVID-19 pandemic, which may have affected provider treatment and airway management preferences. Each of these factors strongly limits the generalizability of our findings.

5 | DISCUSSION

This study supports the favorable safety profile of prehospital high-dose intravenous NTG use for treating AHFS with APE. The frequency of hypotension (1.3%) is similar to values documented in prior prehospital[21,22] and hospital-[10,11,23,24] based studies. Furthermore, this hypotension was transient, with no documented associated arrhythmia or altered mentation. The median absolute SBP reduction observed in this study was 15%, which is within accepted parameters for acute blood pressure management in hypertensive emergency.[25]

Prior work has highlighted fears that paramedics cannot accurately and safely identify AHFS exacerbations with APE.[26,27] However, more recently published data suggest that paramedics can accurately identify decompensated APE and that prehospital high-dose intravenous NTG use is feasible.[21,22] We believe that our prior success may stem from the intensive educational program developed in conjunction with this protocol. Specifically, we addressed the differentiation of AHFS with APE from obstructive lung disease exacerbation by multiple historical, exam, and vital sign factors. The acuity of onset, high-risk

TABLE 4 Vital signs for subgroups with and without SL NTG and/or NIPPV before IV nitroglycerin administration and at presentation to the emergency department. Presented as median (IQR).

	+SL NTG/+NIPPV ($n = 43$)			+SL NTG/-NIPPV ($n = 24$)			−SL NTG/+NIPPV ($n = 120$)			−SL NTG/-NIPPV ($n = 48$)		
	Initial EMS	Final EMS	Median change	Initial EMS	Final EMS	Median change	Initial EMS	Final EMS	Median Change	Initial EMS	Final EMS	Median change
Systolic blood pressure, mmHg	203 (178, 224)	168 (157, 183)	−30 (−56, −11)	18 (172, 204)	159 (141, 174)	−29 (−52, −21)	200 (179, 200)	169 (146, 191)	−29 (−51, −7)	202 (185, 220)	168 (144, 202)	−24 (−47, −15)
Diastolic blood pressure, mmHg	105 (90, 125)	91 (75, 105)	−15 (−34, −1)	107 (89, 126)	88 (79, 100)	−24 (−39, −1)	104 (94, 106)	90 (79, 106)	−14 (−29, 0)	110 (99, 126)	93 (99, 111)	−17 (−29, −2)
Heart rate, bpm	108 (87, 124)	102 (80, 115)	−5 (−12, 1)	104 (94, 120)	105 (92, 116)	−1 (−7, 5)	110 (95, 125)	103 (88, 123)	−6 (95, 123)	104 (80, 127)	103 (76, 114)	−5 (−17, 2)
Oxygen saturation, %	88 (81, 94)	98 (97, 99)	8 (5, 16)	91 (85, 97)	96 (95, 98)	4 (2, 10)	89 (82, 95)	98 (96, 99)	9 (1, 15)	92 (83, 96)	97 (95, 98)	6 (0, 13)

Abbreviations: bpm, beats per minute; IV, intravenous; NIPPV, non-invasive positive pressure ventilation; NTG, nitroglycerin; SL, sublingual.

past medical history (hypertension, end-stage renal disease, and known CHF), presence of rales on auscultation, and waveform capnography use were all emphasized as considerations making AHFS with APE more likely in patients presenting with elevated blood pressure and moderate to severe respiratory distress.

Additional potential benefits of bolus dose intravenous NTG are its relatively low cost and simplicity of dosing and administration. We used a 100 mcg/mL concentration with a final volume of 10 mL. Our system cost for a single intravenous NTG bottle was approximately $20. Two-thirds of the patients required only a single 1 mg dose, consistent with prior hospital and EMS studies.[11,21,22]

Although there is no current prehospital comparison of sublingual to intravenous NTG, prior EMS evidence suggests a minimal hemodynamic impact of sublingual NTG on blood pressure when used to treat pain in ST-elevation myocardial infarction[28] or when treating prehospital CHF.[17] ED and ICU studies have found that intravenous NTG improves morbidity by reducing the incidence of intubation and mechanical ventilation, and the beneficial effects are more pronounced with high-dose bolus administration and less so with continuous NTG drip.[10,11] Recent data from Miro et al. even suggest mortality benefits, specifically from EMS administration of intravenous NTG.[23] Thus, we feel strongly that intravenous bolus NTG should be considered as a first-line pharmacologic treatment for critically ill, AHFS-induced APE by EMS clinicians. We encourage additional prospective investigations on its morbidity and mortality effects in the EMS setting.

In conclusion, this study provides additional evidence that high-dose intravenous NTG may be safe for use by paramedics treating decompensated AHFS with APE. A hypotension rate of less than 2% was noted after intravenous NTG administration, and adequate blood pressure reduction in the setting of hypertensive emergency was also demonstrated (Figure 3). More extensive, multiservice, prospective prehospital studies are needed to investigate further bolus-dose intravenous NTG's effect on morbidity and mortality in decompensated AHFS with APE.

AUTHOR CONTRIBUTIONS

All authors have made substantial contributions to the conception and design of the study (Casey Patrick, Louis Fornage, Brad Ward, Michael Wells, Kevin Crocker, Kelly Rogers Keene, Sara Andrabi, Robert Dickson), acquisition of data (Casey Patrick, Brad Ward, Michael Wells, Kevin Crocker), analysis and interpretation of data (Casey Patrick, Brad Ward, Michael Wells, Kevin Crocker, Robert Dickson), and drafting/revising it critically for important intellectual content (Casey Patrick, Louis Fornage, Brad Ward, Michael Wells, Kevin Crocker, Kelly Rogers Keene, Sara Andrabi, Robert Dickson). All authors have read and approved the submitted manuscript.

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CONFLICT OF INTEREST STATEMENT

No conflicts of interest to report.

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